o-Benzenedisulfonimide as a Reusable Brønsted Acid Catalyst for Hetero-Michael Reactions

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o-Benzenedisulfonimide as a Reusable Brønsted Acid Catalyst for Hetero-Michael Reactions

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Abstract

The hetero-Michael reactions between various oxygen, sulphur and nitrogen nucleophiles and α,β-unsaturated compounds were carried out in the presence of catalytic amounts of *o*-benzenedisulfonimide as Brønsted acid organocatalyst. The reaction conditions were very mild and the yields of target products were good. The catalyst was easily recovered and purified, ready to be used in further reactions. This ability grants economic and ecological advantages.

Introduction

The conjugate addition of oxygen, nitrogen and sulphur nucleophiles to unsaturated carbonyl compounds by Michael reaction is one of the most advantageous and easy methods for the forming of C-O, C-N and C-S bonds in organic synthesis.[1]

In fact β-amino[2a,b] and β-oxy carbonyl groups[2a,c] are important functionalities presents in numerous natural organic compounds such as alkaloids and polyketides. β-Amino carbonyl compounds are also the key intermediates for the synthesis of amino alcohol and β-amino acid derivatives which possess various biological activities.[3] Moreover, thio-Michael addition has emerged as one of the most powerful tools for C-S bond formation;[4] in fact thio-Michael addition provides a widespread synthetic utility in many organic processes[5a-c] and in the synthesis of medicinally important compounds.[5d]

Many different catalysts have been applied in hetero-Michael additions[1] and, in particular, a number of Lewis acids.[6] The main disadvantages of many of these methods are the harsh reaction conditions, the relatively long reaction times, the low selectivity and often the use of toxic, corrosive and expensive catalysts in high loading. Moreover their recovery and reuse is often impossible. To overcome this, hetero-Michael additions have been successfully performed in acidic ionic liquids (2-hydroxyethylammonium formate,[7a] 1-(4-sulfobutyl)piridinium sulfate,[7b] ethyl-*n*-butylphosphonium tosylate,[7c] *N*-methyl-2-pyrrolidonium dihydrogen phosphate[7d]) and very recently it has been reported that 1,4-addition of anilines to Michael acceptors proceeds easily in protic solvents[8a] or in water[8b] without any catalyst. Moreover it was also reported that the aza-Michael reaction between various aliphatic amines and Michael acceptors furnished the Michael adducts in good to excellent yield, without any solvent or catalysts.[8c]

The use of Brønsted acids as homogeneous catalysts is less widespread. Spencer[9a] tested a number of Brønsted acid in aza, oxa and thia-Michael additions obtaining the best results using Tf_2NH; Shen[9b] used TfOH as catalyst in an intramolecular oxa-Michael addition and Goswani[9c] used 15% aqueous HCl in the Michael addition between acrylates and fullerenol in the presence of an ammonium salt as phase transfer catalyst. Furthermore, the literature shows the use of some Brønsted acids as heterogeneous catalysts

(H_2SO_4·SiO_2,[10a] HBF_4·SiO_2,[10b] acidic clays,[10c] Nafion SAC-13,[10d] polystyrenesulfonic acid[10e] and $HClO_4$·SiO_2[10f]) in several hetero-Michael additions.

We have recently reported the use of *o*-benzenedisulfonimide[11a] (**1**, Figure 1) in catalytic amounts as a safe, non-volatile and non-corrosive Brønsted acid in several acid-catalyzed organic reactions.[11b] The catalyst, that belongs to a high acidity (pk_a -4.1 at 20 °C),[11a] was easily recovered and purified, ready to be used in further reactions, with economic and ecological advantages.

Figure 1. *o*-Benzenedisulfonimide

Results and Discussion

In this paper we wish to propose the use of **1** as a reusable Brønsted acid catalyst for the hetero-Michael addition reactions between oxygen **2**, sulphur **3** or nitrogen **4** nucleophiles and several α,β-unsaturated compounds **5–9** (Scheme 1).

Scheme 1. *o*-Benzenedisulfonimide **1** as a catalyst for hetero-Michael reactions

Initially, in order to optimize the reaction conditions, the model reaction between methyl vinyl ketone (**5**) and benzyl alcohol (**2a**) at r.t. and in the presence of **1** as catalyst was studied under different conditions. As reported in Table 1 (entries 1–4), polar, slightly polar solvents or H_2O were tested but the best results were obtained in solvent-free reaction conditions (entries 5–7). The effect of the catalytic amount of **1** was also studied. So, in the best conditions, an excellent yield (92%) of Michael adduct **10a** was achieved in a short reaction time (1 h) under solvent-free conditions and in the presence of 5 mol % of **1** (entry 7).

Table 1. Trial reactions between **2a** and **5**

Furthermore, **1** was recovered in excellent yields (89%) by simply evaporating the aqueous washings under reduced pressure. The recovered **1** was reused as the catalyst in another five

consecutive runs between **2a** and **5**. The results are listed in Table 2. The yields of **10a** and the recovery of **1** were always good throughout the course of the different runs.

Table 2. Consecutive runs with recovered **1**

The high yield, short reaction time and simplicity of the procedure encouraged us to further exploit the generality and the scope of this reaction, catalyzed by **1**, using other alcohols **2** and other nucleophiles like thiols **3**. The results are collected in Table 3. The Michael addition of various alcohols **2b**–**e** to **5** produced the corresponding adducts **10b**–**e** in excellent yields (Table 3, entries 2–5) On the other hand, no reactions occurred when less reactive phenols **2f, g** were used (Table 3, entries 6, 7). Also the reaction of aliphatic or aromatic thiols **3a**–**e** with **5** gave the corresponding adducts **11a**–**e** in very high yields without any by-product (Table 3, entries 8–12). It must be stressed that thiols can react without a catalyst.[4c] However, the reaction time was longer. (Table 3, entry 13)

Table 3. Hetero-Michael reaction between **5** and alcohols **2** or thiols **3**

In order to explore the synthetic usefulness of **1** in oxa-Michael and thia-Michael reactions further, we also investigated the reactions of four other types of α,β unsaturated compounds **6**–**9** with selected **2** or **3**. The reaction between **2a** and **6** furnished **10h** in very good yields (Table 4; entry 1). However, it must be stressed that the reactions of the weak nucleophile **2a** with **7**–**9** did not proceed at all, even at 50 °C (Table 4; entries 2–4). Thiols **3a** and **3e** reacted easily at r.t. or when heated to 50 °C with **6** and **7** (Table 4; entries 5–7), whereas no results were obtained with **8** and **9** (Table 4; entries 8–9). All these examples demonstrates the usefulness and the simplicity of this method since it requires mild reaction conditions and short reaction times; the target products are obtained in good yields and good selectivity and the absence of by-products is observed.

Table 4: Hetero-Michael reaction between **6**–**9** and alcohol **2a** or thiols **3a, 3e.**

In order to further expand the scope of our work, we decided to study the aza-Michael addition too. To start, we tested the reaction between **4a** and **5** as reported in Table 5. First of all, it was necessary to cool at 0 °C (Table 5, entry 2) to minimize the formation of two by-products, namely imine **13a** (that formed as a result of nuchleophilic attack of **4a** on the carbonyl group of **5**) and adducts **14a** (that formed as a result of the further nucleophilic attack of **12a** on **5**; Table 5, entry 1). On the contrary, no side products were detected using the less nucleophilic aniline **4e** (Table 5, entry 6). Also the reaction of other aliphatic amines **4b–d** gave the corresponding Michael adducts **12 b–d** in good yields and short reaction times (Table 5, entries 3–5).

Table 5: Hetero-Michael reaction between **5** and amines **4**

Finally, amines **4a, b, e**, stronger nucleophiles than **2** or **3**, reacted easily at r.t. or at 50 °C with **6–9** (Table 6; entries 1–3, 6, 8–10) producing the adduct **12f–l** in good yields. It must be stressed that the reactions between **4a, b** and **9** furnished the immines **15a, b** that derived from Michael adducts after the loss of nitromethane (Table 6; entries 11–12).

Table 6: Hetero-Michael reaction between **6–9** and amines **4a, b, e.**

In the literature it is reported that the aza-Michael reaction proceeds without any catalyst, reacting various aliphatic amines with a number of Michael acceptors.[8c] For example, the reaction between benzyl amine and methyl acrylate furnishes after 18 hours at r.t. a mixture of mono and di-Michael adducts (in total 90% yield). On the contrary, aniline does not react in these conditions. In the light of these, performing the reaction between **4a, e** and **7** without **1** we obtained about the same results reported in the literature (Table 6; entries 4, 7). From our experimental data it was evident that the presence of catalyst **1** significantly accelerated the reaction between **4a** and **7** (Table 6, entry 3), allowed the reaction between **7** and weaker nucleophile **4e** (Table 6, entry 6) and prevented the formation of the di-adduct. It is reasonable to assume to have a protonation of amine **4a** by strong acid **1**, with the formation of ammonium salt **16**. Despite this, **4a** and **7** reacted very fast. So, we

prepared the ammonium salt **16** and used it as a catalyst in the reaction between **4a** and **7**. We obtained the Michael adduct **12h** with a yield and time comparable to those obtained for the reaction performed with **1** (Table 6; entry 5). In the light of these, it can be assumed that **16** transfers a proton on the carbonyl group of the Michael acceptor **7**. The stable intermediate **17** reacts very easily with **4a** to give **12h** (Scheme 2). However, due to the high stability of the cation **17**, the direct protonation of **7** by **1** can not be excluded, even in the presence of **4a**. Finally, the absence of the possible di-adduct *N,N*-bis(2-ethoxycarbonylethyl)benzylamine could be explained by the higher rate, in the presence of a catalyst, of the reaction between **4a** and **7**. Clearly, also in all the other aza-Michael reactions conducted with aliphatic amines, it could be assumed that ammonium salt of **1** acts as a catalyst, activating the Michael acceptors.

Scheme 2. Aza-Michael reaction catalyzed by **16**

In conclusion, in this paper the synthetic usefulness of *o*-benzenedisulfonimide (**1**) as a catalyst in hetero-Michael reactions has been demonstrated. The advantages of the method are mild solvent-free reaction conditions, stoichiometric reagent ratios, catalytic amount of the readily available and easy-handling Brønsted acid catalyst. Furthermore, in comparison with other catalysts extensively used for hetero-Michael reactions, **1** turned out to be a safe, non-volatile, non-corrosive and bench-stable catalyst. A further valuable aspect of the use of **1** is its easy recovery in high yield from the reaction mixture, due to its complete solubility in water, and its reuse without loss of catalytic activity in other reactions.

Experimental

4-Benzyloxybutan-2-one (10a): representative procedure for the preparation of Michael adducts 10, 11, 12: *o*-Benzenedisulfonimide (**1**; 5 mol %; 55 mg, 0.25 mmol) was added to a mixture of benzyl alcohol (**2a**; 0.54 g, 5 mmol) and methyl vinyl ketone (**5**; 0.36 g, 5 mmol) The

mixture was stirred at r.t. The reaction was monitored by GC and GC-MS until the complete disappearance of **2a** and **5** (1 hours). The reaction mixture was poured into Et_2O-H_2O (50 ml, 1:1). The aqueous layer was separated and extracted with Et_2O (2 x. 50 ml). The combined organic extracts were washed with H_2O (2 x. 50 ml), dried over Na_2SO_4. After solvent removal under reduced pressure, the crude residue was the virtually pure (GC, GC-MS, ^{1}H NMR, ^{13}C NMR) title compound **10a**. The aqueous layer and aqueous washings were collected and evaporated under reduced pressure. After removal of the water, virtually pure (^{1}H NMR) *o*-benzenedisulfonimide (**1**) was recovered (49 mg, 89 % yield).

The recovered **1** was employed in other five catalytic cycles under the conditions above described, reacting with **2a** and **5**; Table 2 reported the yields of **10a** and the yields of recovered **1**.

Supplementary Material: General experimental details; physical and spectral data of the products **10,11,12**; preparation, physical and spectral data of product **16**; more details for Tables 5 and 6.

Acknowledgments

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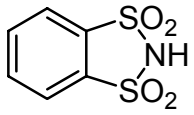
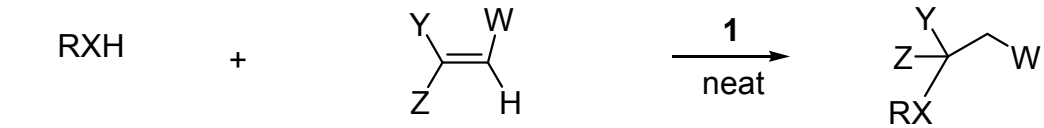


1

Figure 1. *o*-Benzenedisulfonimide

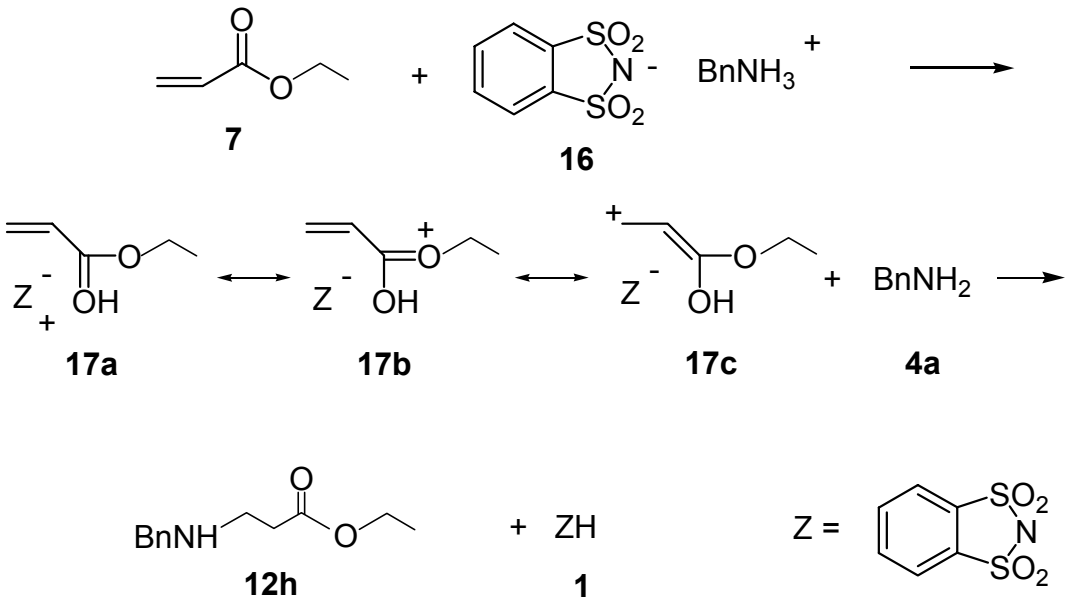


2: X= O
3: X= S
4: X= NH

5: Y,Z= H; W= COMe
6: Y=H; Z= Me; W= COEt
7: Y,Z= H; W= COOEt
8: Y,Z= H; W= CN
9: Y= H; Z= Ph; W= NO_2

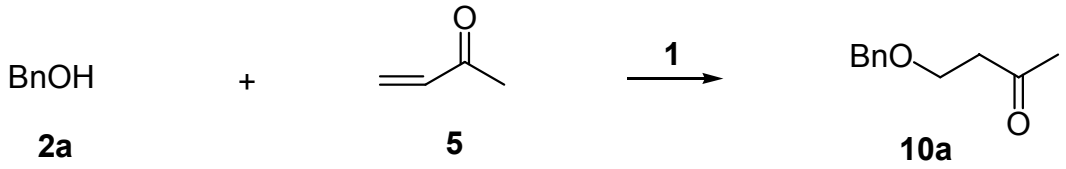
10: X= O
11: X= S
12: X= NH

Scheme 1. *o*-Benzenedisulfonimide **1** as a catalyst for hetero-Michael reactions



Scheme 2. Aza-Michael reaction catalyzed by **16**

Table 1. Trial reactions between **2a** and **5**



2a **5** **10a**

Entry	Solvent	**1** mol-%	Time (h)	Yield (%) of **10a**[a]
1	MeCN	5	24	42[b]
2	CH_2Cl_2	5	6	90[c]
3	Toluene	5	24	35[b]
4	H_2O	5	24	Traces[d]
5	neat	1	5	87[c]
6	neat	2	3	89[c]
7	neat	5	1	92[c]

[a]Yields refer to the pure products.

[b]After 24 h, unreacted **2a** and **5** were detected by GC and GC-MS. Nevertheless, the reaction was stopped and the crude residue, purified in a silica gel chromatography column, (eluent: PE/Et_2O 9.8:0.2), afforded pure **10a**.

[c]On the GC, GC-MS and NMR analyses, the crude residue was the virtually pure **10a**.

[d]After 24 h, unreacted **2a** and **5** were detected by GC and GC-MS. Only weak traces of **10a** were detected.

Table 2. Consecutive runs with recovered **1**

Entry	Time (h)	Yield (%) of **10a**[a]	Recovery (%) of **1**
1	1	92[b]	89, 49 mg[c]
2	1	85	86, 42 mg[d]
3	1	85	86, 42 mg[e]
4	1.5	82	81, 34 mg[f]
5	1.5	83	79, 27 mg[g]
6	2.5	80	74, 20 mg

[a]Yields refer to the pure products.

[b]The reaction was performed with 5 mmol of **2a** and **5** and 5 mol-% of **1** (55 mg, 0.25 mmol).

[c]Recovered **1** was used as a catalyst in entry 2.

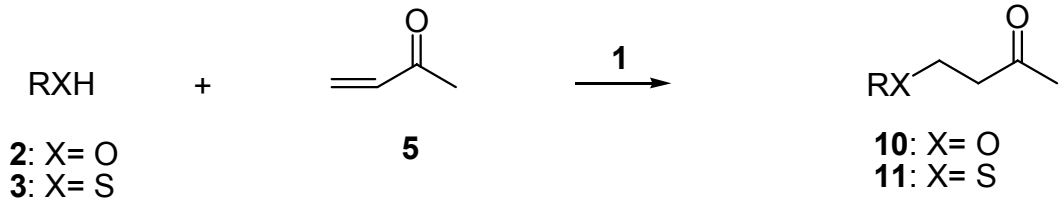
[d]Recovered **1** was used as catalyst in entry 3.

[e]Recovered **1** was used as a catalyst in entry 4.

[f]Recovered **1** was used as a catalyst in entry 5.

[g]Recovered **1** was used as catalyst in entry 6.

Table 3. Hetero-Michael reaction between **5** and alcohols **2** or thiols **3**



Entry	R	Products and Yields (%)[a,b]	Temp. (°C)	Time (h)
1	Bn; **2a**	**10a**; 92[c]	r.t.	1
2	*n*Bu; **2b**	**10b**; 85[c]	r.t.	1
3	*s*Bu; **2c**	**10c**; 88[c]	r.t.	1
4	*t*Bu; **2d**	**10d**; 82[c]	r.t.	1
5	Cy; **2e**	**10e**; 84[c]	r.t.	1
6	Ph; **2f**	**10f**; -	50	24
7	4-$MeOC_6H_4$; **2g**	**10g**; -	50	24
8	Bn; **3a**	**11a**; 87[c]	r.t.	0.5
9	*n*Bu; **3b**	**11b**; 91[c]	r.t.	0.5
10	*s*Bu; **3c**	**11c**; 85[c]	r.t.	0.5
11	*t*Bu; **3d**	**11d**; 82[c]	r.t.	0.5
12	Ph; **3e**	**11e**;92[d]	r.t.	0.5

13	Ph; **3e**	**11e**;90[d,e]	r.t	3

[a]All the reactions were performed with 5 mol-% of **1**; the reactants are in equimolar amounts (5 mmol).

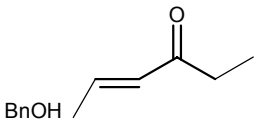
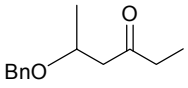
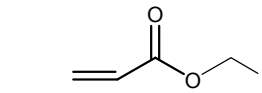
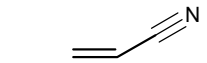
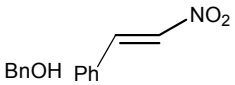
[b]Yields refer to the pure and isolated products.

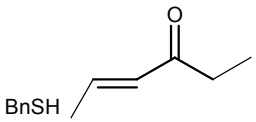
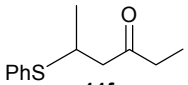
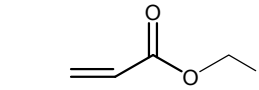
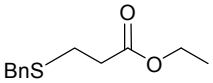
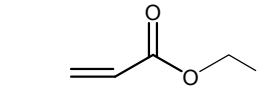
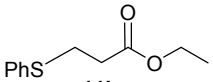
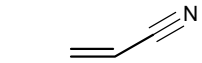
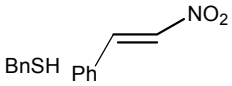
[c]On the GC, GC-MS and NMR analyses, the crude residues were the virtually pure hetero-Michael adducts **10,11**.

[d]The crude residue was purified in a silica gel chromatography column (eluent: PE/Et_2O 9.8:0.2).

[e]The reaction was performed without catalyst **1**.

Table 4. Hetero-Michael reaction between **6–9** and alcohol **2a** or thiols **3a, 3e**

Entry	Reactants	Products and Yields (%)[a,b]	Temp.(°C)	Time (h)
1	 BnOH **2a** **6**	 **10h** 82[c]	r.t	2
2	 BnOH **2a** **7**	-	50	24
3	 BnOH **2a** **8**	-	50	24
4	 BnOH **2a** **9**	-	50	24

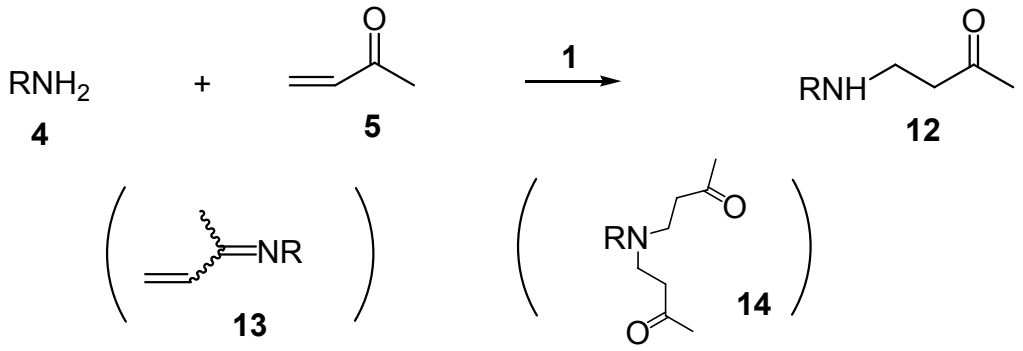
5	 BnSH **3a** **6**	 **11f**	88[c]	r.t.	1
6	 BnSH **3a** **7**	 **11g**	77[c]	50	1
7	 PhSH **3e** **7**	 **11h**	*80*[c]	50	1
8	 BnSH **3a** **8**		-	50	24
9	 BnSH Ph **3a** **9**		-	50	24

[a]All the reactions were performed with 5 mol-% of **1**; the reactants are in a equimolar amounts (5 mmol).

[b]Yields refer to the pure and isolated products.

[c]On the GC, GC-MS and NMR analyses, the crude residues were the virtually pure hetero-Michael adducts **10**, **11**.

Table 5. Hetero-Michael reaction between **5** and amines **4**



Entry	R	Products and Yields (%)[a,b]	Temp. (°C)	Time (h)
1	Bn; **4a**	[c]	r.t	0.5
2	Bn; **4a**	**12a**; 85[d]	0	0.5
3	*n*Bu; **4b**	**12b;** 82[d]	0	0.5
4	*s*Bu; **4c**	**12c**; 82[d]	0	0.5
5	*t*Bu; **4d**	**12d**; 77[d]	0	0.5
6	Ph; **4e**	**12e**; 89[e]	r.t.	1

[a]All the reactions were performed with 5 mol-% of **1**; the reactants are in equimolar amounts (5 mmol).

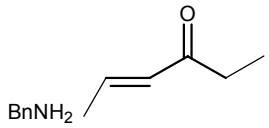
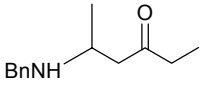
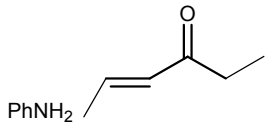
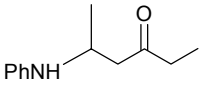
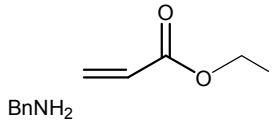
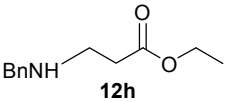
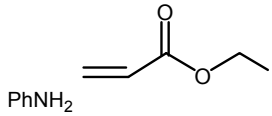
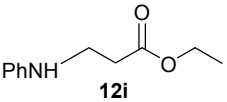
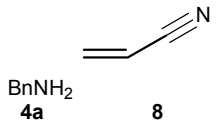
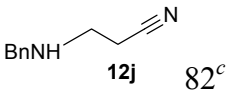
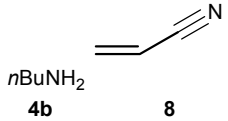
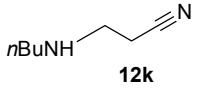
[b]Yields refer to the pure and isolated products.

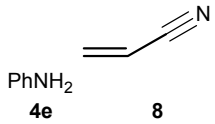
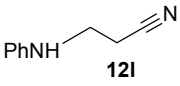
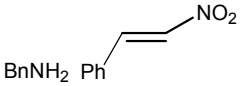
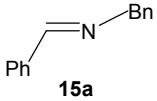
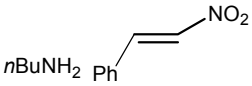
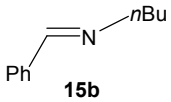
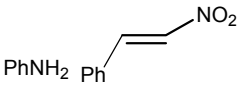
[c]On the GC and GC-MS analyses of the crude residue, three products were detected: **12a, 13a** and **14a**. However, it was impossible to separate them by chromatography column.

[d]On the GC and GC-MS analyses of the crude residues, weak traces of compounds **13** and **14** were detected. The crude residues, purified in a silica gel chromatography column (eluent: PE/Et_2O 9.8:0.2), afforded pure compounds **12**.

[e]The crude residues were purified in a silica gel chromatography column (eluent: PE/Et_2O 9.8:0.2). For more details see also Supplementary Material.

Table 6. Hetero-Michael reaction between **6–9** and amines **4a, b, e**

Entry	Reactants	Products and Yields (%)[a,b]	Temp.(°C)	Time (h)
1	 **4a** **6**	 **12f** 86[c]	0	1
2	 **4e** **6**	 **12g** 82[d]	r.t.	4
3	 **4a** **7**	 **12h** 80[c]	r.t	1
4	**4a**	**7**[e]	[f]	r.t.	24
5	**4a**	**7**[g]	**12h** 82[c]	r.t.	1
6	 **4e** **7**	 **12i** 65[d]	50	24
7	**4e**	**7**[e]	**-**	50	24
8	 **4a** **8**	 **12j** 82[c]	r.t.	2
9	 **4b** **8**	 **12k** 85[c]	50	1

10	 **4e** **8**	 **12l**	67[d]	50	24
11	 **4a** **9**	 **15a**	82[d]	50	2
12	 **4b** **9**	 **15b**	85[d]	50	2
13	 **4e** **9**	*f*		50	24

[a]All the reactions were performed with 5 mol-% of **1**; the reactants are in equimolar amounts (5 mmol).

[b]Yields refer to the pure and isolated products.

[c]On the GC, GC-MS and NMR analyses, the crude residues were the virtually pure hetero-Michael adducts **12**.

[d]The crude residues were purified in a silica gel chromatography column; eluent: PE-Et_2O (9.8:0.2).

[e]The reaction was performed without catalyst **1**.

[f]On the GC and GC-MS analyses of the crude residue, two products were detected: **12h** and *N,N*-bis(2-ethoxycarbonylethyl)benzylamine. However, it was impossible to separate them by chromatography column.

[g]The reaction was performed using the benzylammonium salt **16** as catalyst (5 mol-%; 81.5 mg).

[h]On the GC and GC-MS analyses of the crude residue two products were detected: *N*-benzylideneaniline (**15c**) and *N*-(1-phenyl-2-nitroethyl)aniline. However, it was impossible to separate them by chromatography column. For more details see also Supplementary Material.